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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/520,760	03/07/2000	Krishan L. Taneja	BP9806US-CP1	9118

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EXAMINER
SOUAYA, JEHANNE E

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 04/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/520,760	TANEJA, KRISHAN L.	
	Examiner	Art Unit	
	Jehanne E Souaya	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *26 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5/2001* .
4) ☒ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Continuation of Disposition of Claims: Claims pending in the application are 1, 2, 10, 11, 12, 29, 31, 33, 34, 38, 39, 40,45, 47, 49, 50, 54, 55, 56, 64, 65, 66, 78, 79, and 80. '. ;.
Continuation of Disposition of Claims: Claims withdrawn from consideration are 1,2,29,31,33,34,38-40,45,47,49,50,54-56,64-66 and 78-80.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group XIV in the Paper dated 8/6/2002 is acknowledged. The traversal is on the ground(s) that it is not proper to restrict a Markush group and that the instant claims are in proper Markush format because they exhibit a common property. These arguments have been thoroughly reviewed but were not found persuasive. As previously stated, the function of the sequences, that is, the ability to hybridize to a specific chromosome is dependent on its structure, that is, it's nucleobase composition. Although this nucleobase containing portion is not a nucleic acid, it functions in hybridization through Watson Crick or Hoogstein base pairing and recognizes a DNA sequence through its ability to hybridize using Watson Crick or Hoogstein base pairs. A probe, whether nucleic acid or PNA, which comprises a nucleobase containing portion as outlined in SEQ ID NO 1 and specifically detects chromosome X is patentably distinct from a probe, whether nucleic acid or PNA, which comprises a nucleobase containing portion as outlined in SEQ ID NO 10, and specifically detects chromosome Y. These probes have different functions, and presumably, as the specification teaches that they are specific for specific chromosomes, the probe with a nucleobase containing portion of SEQ ID NO 1 will not detect chromosome Y. Probes that detect chromosome X are not functionally equivalent to probes that detect chromosome Y. The response asserts that the claims are generic in nature. This argument was not found persuasive because, as set forth in the specification, the probing nucleobase sequence is the sequence recognition portion of the construct (see p. 19, lines 26-27) and is responsible for the function of the molecule. Further, the specification teaches that each nucleobase portion was derived from specific regions for each

specific chromosome (see pp 53-54, "Design of Chromosome Specific Probes"). While a PNA probe with a nucleobase containing portion of SEQ ID NO 1 and a PNA probe with a nucleobase containing portion of SEQ ID NO 10 are both PNAs, a polymerase and a ligase are also both proteins, however they are patentably distinct because the specific composition of amino acids for each molecule make them structurally and functionally different. In addition, the search burden for searching all 118 sequences is extremely high for both the examiner and the office. Therefore, the requirement is still deemed proper and is therefore made FINAL.

It is noted that the response to the restriction requirement does not specify which probes have been elected. Group XIV, as outlined in the previous office action, is subject to further restriction because the probe set comprising SEQ ID NOS 1 and 10 is patentably distinct from a probe set comprising SEQ ID NOS 2 and 11. The nucleobase containing portions are directed to different regions of chromosomes X or Y, respectively, and are structurally distinct chemical compounds (such was set forth in the previous restriction requirement in the examiner's response, at pages 9-10). Further, the search required for SEQ ID NO 1 and 10 is not required for SEQ ID NOS 2 and 11. In a telephone conversation with Brian Gildea, the examiner indicated that the presumption was that all 118 probes had been elected with group XIV. Mr. Gildea indicated that this was correct. The claims should be amended to reflect such election.

2. Currently, claims 10-12, SEQ ID NOS 1-118 are under consideration at this time. An action on the merits, follows.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 10-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a probe set comprising PNA probes with N-[2-(aminoethyl)] glycine backbones consisting of nucleobases of SEQ ID NOS 1-118, does not reasonably provide enablement for a probe set comprising any non nucleic acid probes for chromosomes X, Y, 1-3, 6, 8, 10-12, and 16-18 or a probe set comprising any non nucleic acid probes "having" a nucleobase containing portion of SEQ ID NOS 1-118, or to a probe set comprising non nucleic acid probes "having" a probing nucleobase sequence at least a portion of which is at least ninety percent homologous to the nucleobase sequence or their complements of SEQ ID NOS 1-118. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are broadly drawn to any probe set comprising any *non nucleic acid* probes for chromosomes X, Y, 1-3, 6, 8, 10-12, and 16-18, or to a probe set comprising non nucleic acid probes "having" a probing nucleobase sequence at least a portion of which is at least ninety percent homologous to the nucleobase sequence or their complements of SEQ ID NOS 1-118, or a probe set comprising any *non nucleic acid* probes "having" a nucleobase containing portion of SEQ ID NOS 1-118.

The specification defines "non nucleic acid probes" as a probe comprising a probing nucleobase sequence which is designed to hybridize to at least a portion of a target sequence, such as a PNA probe. The specification further defines "PNA" as any oligomer, linked polymer, or chimeric oligomer, including PNA-DNA chimeras, comprising two or more PNA subunits, nucleic acid mimics, and peptide based nucleic acid mimics. The specification teaches that a use for the probes of the claimed invention are for improving the specificity, sensitivity and reliability of probe based assays for the detection of chromosomes X, Y, 1-3, 6, 8, 10-12, and 16-18. The specification teaches the specific constructs of table 2 with the specific nucleobase containing portions outlined in the specification, that is "consisting" of SEQ ID NOS 1-118. The specification demonstrates the use of such as probes as chromosome specific probes. However, the claims are of a much broader scope, such that the specification does not enable the skilled artisan to predictably make or use the claimed products in methods of detecting, identifying, or enumerating specific chromosomes.

The specification teaches that the nucleobase sequence of the non nucleic acid probes is the sequence recognition portion of the construct. However, as outlined above, the term "non nucleic acid probes" encompasses a large number of different types of molecules which the specification has not demonstrated any predictable use for in detecting, identifying or enumerating specific chromosomes. Probes encompassed by all of the claims include for example, PNA probes of undefined length, and PNA-DNA chimeras. It is known, however, that in PNA-DNA chimeras both the PNA nucleobase portion and the DNA portion are involved in hybridization. Therefore, while the specific probes of table 2 have been shown to be specific for identifying a chromosome, it is unpredictable as to whether longer sequences which can

comprise an unlimited number of any bases, either PNA or DNA, as illustrated by the broad definitions in the specification, would also exhibit the same properties. While the skilled artisan would be able to envision some constructs that would seemingly be specific for a particular chromosome using sequence comparison with the sequences in Genbank, the specification teaches that in functional assays, "many of the sequences originally chosen did not prove to be highly specific despite alignment analysis indications that they should be specific to the chromosome sought to be detected" (see p. 25, lines 2-4). Therefore, the specification teaches of the unpredictability in designing chromosome specific probes. Given such teachings, the skilled artisan would not be able to predictably determine the identity of the probing nucleobase containing portions of the probes encompassed by claims 10 and 11 which would be able to function in identifying, detecting, or enumerating human chromosomes X, Y, 1-3, 6, 8, 10-12, and 16-18 in a sample, other than by specific SEQ ID NO. Further, while it is known that PNA oligomers hybridize stably with DNA, the art teaches that PNA-DNA chimeras do not share these properties, although theoretical models indicated that they should. For example, Petersen et al (Bioorganic & Medicinal Chemistry Letters, vol 5, pp 1119-1124; 1995) teach that PNA-DNA chimeras hybridize less efficiently to complementary DNA than the parent DNA oligomers indicating that the PNA-DNA 3' junction is not structurally optimal despite a favorable configuration by model building (see p 1123, 2nd para). The post filing date art also illustrates such unpredictability. For example, Capasso et al (Tetrahedron, vol. 57, pp 9481-9486; 2001) teaches that the affinity of PNA DNA chimeras towards target DNA was quite affected by the PNA structure, exhibiting changes in melting temperature of + or – 2 degrees C compared with all DNA sequences, and that such did not appear to be easily explainable (see p. 9483, col. 2, 2nd

full para). Capasso also teaches that further experimentation was being undertaken to gain a deeper insight into the behavior of such chimeras. Therefore, the art illustrates the unpredictability that would be involved for the skilled artisan to make and use the large number of different types of probes encompassed by the broad scope of the claimed invention.

Claim 10 encompasses products with no specifically defined structure, and such products, while being able to detect a certain chromosome would not necessarily be specific for detecting chromosome X, for example. Probes having a probing nucleobase sequence of undefined length wherein only a portion are 90% homologous to the nucleobase sequence of SEQ ID NO 1 (claim 11) encompasses a probe with only 1 nucleobase in common with SEQ ID NO 1, wherein it is unpredictable as to whether such a probe would be able to be used to detect chromosome X. Claim 10 necessarily encompasses such sequences as claim 11 is dependent from claim 10. Claim 12, although drawn to exact probing nucleobase sequences (that is, the claim does not encompass sequences, either PNA or DNA or nucleic acid mimics, etc, on either side of the sequence identifier), encompasses probes (due to the broad definitions of "non nucleic acid probes" and "PNA" as outlined in the specification) wherein the specific nucleobase containing portion is a DNA-PNA chimera, for example. However, due to the lack of guidance from the specification and the unpredictability taught in the art, further, undue experimentation would be required of the skilled artisan to make and use the extremely large number of different molecules encompassed by the broad scope of the claimed invention. A large amount of unpredictable trial and error analysis would be required for the skilled artisan to make and use probes as encompassed by the claims. Such experimentation is considered undue.

5. Claims 10-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to any probe set comprising any *non nucleic acid* probes for chromosomes X, Y, 1-3, 6, 8, 10-12, and 16-18, or to a probe set comprising non nucleic acid probes "having" a probing nucleobase sequence at least a portion of which is at least ninety percent homologous to the nucleobase sequence or their complements of SEQ ID NOS 1-118, or a probe set comprising any *non nucleic acid* probes "having" a nucleobase containing portion of SEQ ID NOS 1-118.

The specification defines "non nucleic acid probes" as a probe comprising a probing nucleobase sequence which is designed to hybridize to at least a portion of a target sequence, such as a PNA probe. The specification further defines "PNA" as any oligomer, linked polymer, or chimeric oligomer, including PNA-DNA chimeras, comprising two or more PNA subunits, nucleic acid mimics, and peptide based nucleic acid mimics. The specification teaches that a use for the probes of the claimed invention are for improving the specificity, sensitivity and reliability of probe based assays for the detection of chromosomes X, Y, 1-3, 6, 8, 10-12, and 16-18. The specification teaches the specific constructs of table 2 with the specific nucleobase containing portions outlined in the specification, that is "consisting" of SEQ ID NOS 1-118. The specification demonstrates the use of such probes as chromosome specific probes. However, the claims, which recite "non nucleic acid probe", encompass a broad genus of probes including not only PNAs, but PNA-DNA chimeras, nucleic acid mimics, and peptide based nucleic acid

mimics. The specification does not teach of any PNA-DNA chimeras, general nucleic acid mimics or peptide based nucleic acid mimics which comprise a probing nucleobase portion which detects a specific chromosome.

The specification teaches that the nucleobase sequence of the non nucleic acid probes is the sequence recognition portion of the construct. However, as outlined above, the term "non nucleic acid probes" encompasses a large number of different types of molecules which the specification has not demonstrated as specific for any particular chromosome. Probes encompassed by all of the claims include for example PNA-DNA chimeras. It is known, however, that in PNA-DNA chimeras both the PNA nucleobase portion and the DNA portion are involved in hybridization. Therefore, while the specific probes of table 2 have been shown to function as specific for identifying a particular chromosome, the specification does not teach of a predictable structure/function correlation between longer sequences which can comprise an unlimited number of any bases, either PNA or DNA, as illustrated by the broad definitions in the specification. While it is known that PNA oligomers hybridize stably with DNA, the art teaches that PNA-DNA chimeras do not share these properties, although theoretical models indicated that they should. For example, Petersen et al (Bioorganic & Medicinal Chemistry Letters, vol 5, pp 1119-1124; 1995) teach that PNA-DNA chimeras hybridize less efficiently to complementary DNA than the parent DNA oligomers indicating that the PNA-DNA 3' junction is not structurally optimal despite a favorable configuration by model building (see p 1123, 2nd para). Additionally, Capasso et al (Tetrahedron, vol. 57, pp 9481-9486; 2001) teaches that the affinity of PNA DNA chimeras towards target DNA was quite affected by the PNA structure, exhibiting changes in melting temperature of + or – 2 degrees C compared with all DNA sequences, and

that such did not appear to be easily explainable (see p. 9483, col. 2, 2nd full para). From such teachings, the skilled artisan would not be able to determine a predictable structure/ function correlation between PNAs and PNA-DNA chimeras, for example, for the purposes of designing chromosome specific probes. Accordingly, the single type of PNA probe (comprising the "E" subunit as defined on page 47) taught in table 2 are not representative of the large genus of different probes which are encompassed by claims.

Further, claim 10, for example, is drawn to probes with no specifically defined probing nucleobase sequences, and claim 11 is drawn to probes with very little specifically defined probing nucleobase sequences (these probes could have as few as 3 or 4 sequential nucleobases in common with any of SEQ ID NOS 1-118). Probes encompassed by these claims include probing nucleobase sequences of undefined length from any part of the genome, including millions of sequences some of which were undefined at the time the specification was filed. However, the probes with sequences outlined in table 2 are not representative of the millions of sequences encompassed by the claims.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 10 and 11 are rejected under 35 U.S.C. 102(e) as being anticipated by Hyldig-Nielsen et al (US Patent 5,985,563, 102(a) date: 11/16/1999; 102(e) date: 5/18/1995).

It is noted that the instant case claims priority from application 09/363,632. The instant claims have been awarded an effective filing date of the 3/7/2000 as the '632 application did not teach or suggest non nucleic acid probes to chromosome 3, 11, or 12.

Claim 10 is drawn to a probe set comprising at least 13 non nucleic acid probes wherein no nucleobase portions are defined. Claim 11 is dependent from claim 10 and is further drawn to non nucleic acid probes wherein a portion of the probes are at least 90% homologous to the sequences set forth in the claims. Hyldig Nielsen teaches a set of PNA probes with a nucleobase containing portion as follows: In table 4, probe 21a comprises the sequence CT, probe 22a comprises the sequence CA, probe 23a comprises the sequence TC, probe 24a comprises the sequence TG, probe 25a comprises the sequence TA, probe 26a comprises the sequence AG, probe 27a comprises the sequence GG, probe 28a comprises the sequence GA, probe 29a comprises the sequence GC, probe 30a comprises the sequence CG, probe 31a comprises the sequence CC, probe 32a comprises the sequence TT, and probe 33a comprises the sequence AT,

wherein these probes are have sequences which are100% homologous with probes 1-118 of claim 11. It is noted that the recitation of "which is suitable for detecting, identifying or enumerating chromosomes X, Y, 1-3, 6, 8, 10-12, and 16-18" is considered an intended use, and has been given no patentable weight.

Conclusion

8. No claims are allowable.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Souaya whose telephone number is (703) 308-6565. The examiner can normally be reached Monday-Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jehanne Souaya

Jehanne Souaya
Patent examiner
Art Unit 1634
4/17/03